## REMARKS/ARGUMENTS

Claims 1-8, 10 and 11 are pending in the present application. Claim 1 is objected to for use of the acronym RAP. This claim has been amended to address the objection. Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Claims 1-3, 7 and 11 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over Yakhyaev *et al.*, *Blood* 90 (10) Suppl. 1:31a (1997). Claims 1-4, 6, 7, 10 and 11 are rejected under §103(a) for allegedly being unpatentable over Yakhyaev *et al.* in combination with Nykjaer *et al., J. Biol Chem.* 267:14543-14546 (1992) and Anderson *et al*, USP 5,840,564. Claims 1-6, 7, 8, 10 and 11 are rejected under §103(a) for allegedly being unpatentable over Yakhyaev *et al.*, Nykjaer *et al*, and Anderson *et al*, further in view of Beguin *et al.*, *Throm Haemost* 78:590-594 (1997). Each of the claim rejections will be addressed below.

***Rejection under 35 U.S.C. § 112, second paragraph***

Claim 2 is rejected as allegedly indefinite for referring to the source of the pro-proteins of blood coagulation in the compositions of the invention. The Examiner objects to this language because it is unclear that proteins derived from the different sources would differ from each other. Applicants respectfully traverse this rejection.

As the Examiner is aware, blood coagulation proteins can be prepared directly from plasma or be produced by recombinant means, in which case the proteins are prepared from a cell culture supernatant. By referring to the source of the proteins, the claim contains a product-by-process limitation describing the manner in which the coagulation proteins are prepared. It is well established that a product-by-process claim, which defines a product in terms of the process by which it is made, is proper (*see* MPEP §2173.05(p)). Since the MPEP specifically states that such claim limitations are proper, the claim language is not indefinite and the rejection should be withdrawn.

***Rejections under 35 U.S.C. § 103(a)***

Claims 1-3, 7 and 11 stand rejected for allegedly being obvious over Yakhyaev *et al.* This rejection is respectfully traversed.

The pending claims are directed to pharmaceutical compositions and methods for treating blood coagulation disorders. The compositions comprise blood coagulation proteins (factor VIII, von Willebrand factor (vWF) or factor V) in combination with a physiologically inert coagulation receptor binding competitor that binds low density lipoprotein receptor-related protein (LRP). The invention is based, at least in part, on the discovery that LRP binding and internalization of blood coagulation proteins is a mechanism by which the plasma levels of these proteins are regulated. As explained below, the prior art failed to provide sufficient evidence of the relevance of this regulatory mechanism.

The primary reference relied upon by the Examiner, the Yakhyaev *et al.* abstract, simply provides preliminary *in vitro* evidence that the A2 domain of factor VIII binds LRP. In the abstract the authors also note that activated protein C (APC) proteolysis of factor VIII is known to regulate factor VIII levels in plasma. Based on the preliminary evidence in the abstract, the authors conclude that LRP-mediated internalization of A2 domains "***may*** represent a ***possible*** complementary mechanism regulating fVIIIa activity" (emphasis added).

To establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria. First, the Examiner must show that there is some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, the Examiner must show a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991) and MPEP § 2142. To support the rejection, the examiner must "present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references." *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985) and MPEP § 2142.

To support the present rejection, the Examiner simply states that, in light of the teaching of Yakhaev *et al*, "it would have been obvious to one of ordinary skill in the art at the time of the invention by the applicant" to prepare the claimed pharmaceutical compositions for

use in treating blood coagulation disorders. As noted above, the law specifically requires a "convincing line of reasoning" to support such a rejection. This the Examiner has not done.

In particular, the Examiner must take into account all of the teachings of the Yakhyaev *et al.* abstract. First, the abstract provides only preliminary *in vitro* evidence of the interaction between the A2 domain and the LRP receptor. Second, APC proteolysis was already known to regulate factor VIII activity. Finally, the authors, themselves, make only a tentative guess that A2 binding may be a complementary mechanism for regulating the levels. In short, the Examiner must provide a convincing line of reasoning as to why one of skill would be motivated to make the present invention in light of the preliminary and tentative teachings in the cited prior art reference.

The Examiner must also explain why one of skill would have a reasonable expectation that inhibiting LPR binding would be effective in increasing blood coagulation protein half life *in vivo* in light of the Yakhyaev *et al.* abstract. Given the complexity of the *in vivo* environment, the Examiner must explain how one of skill could reasonably expect that blocking a single receptor could have a measurable effect on *in vivo* half-life. For example, known mechanisms of clearing factor VIII (*e.g.,* APC proteolysis) could easily overwhelm any effect that blocking LPR binding might have.

Even assuming a *prima facie* case for obviousness is improperly maintained, the Examiner must also consider the evidence in the present application that the claimed invention is surprisingly effective. Example 2 describes experiments in dogs suffering from severe type 3 vWF deficiency, in which a receptor binding competitor (tPA and aprotinin) is administered with vWF. The results of these experiments show that factor VIII activity is increased for 48 hours, even though vWF was essentially eliminated from the plasma by that time point (*see* Figure 2). These results show that factor VIII activity can be enhanced even in the absence of vWF, the natural stabilizer for factor VIII. As explained at paragraph [0025] of the specification, this result was surprising because the results suggest that the receptor binding competitor is able to function as a stabilizer for factor VIII in place of vWF. There is nothing in the cited art to suggest this surprising result.

Similarly, Example 3 describes experiments in which mice lacking endogenous factor VIII are administered RAP prior to the administration of recombinant human factor VIII. The results shown in the table on page 14 demonstrate that factor VIII activity is more than twice as high in these mice compared to control mice receiving only recombinant human factor VIII.

As further evidence that the those of skill regarded the present invention as surprising and unexpected, applicants provide a copy of a paper describing the scientific experimentation supporting the present invention (Schwartz *et al.*, *Blood* 95:1703-1708 (2000)). The fact that this work was published in a prestigious, peer-reviewed journal shows that those of skill considered this work to be an important advance in the understanding of the *in vivo* regulation of factor VIII. It is respectfully submitted that the present invention has significantly advanced the art and provided a new mechanism by which the *in vivo* half life of therapeutic factor VIII can be improved.

In light of the lack of motivation for one of skill to make the claimed invention, the failure of the art to provide a reasonable expectation of success and the surprising results shown in the present application, the rejection of claims 1-3, 7 and 11 is clearly improper. Withdrawal of the rejection is respectfully requested.

The rejection of claims 1-4, 6, 7, 10 and 11 over Yakhyaev *et al.* in combination with Nykjaer *et al.* and Anderson *et al.* is also respectfully traversed. The rejected claims are directed to embodiments of the invention in which the receptor binding competitor is the combination of tPA and aprotinin. Nykjaer *et al.* is cited for teaching that LRP binds tPA. Anderson *et al.* is cited for teaching that tPA activity is inhibited by aprotinin.

Neither secondary reference addresses the deficiencies of the Yakhyaev *et al.* abstract discussed above. In particular, the rejection fails to provide any line of reasoning to show that tPA and aprotinin could reasonably be expected to enhance blood coagulation proteins *in vivo*. As noted in the specification at paragraph [0035], vWF is known to be sensitive to proteolytic degradation by plasmin. tPA is well known to be the physiological activator of plaminogen and thus increasing the levels of plasmin *in vivo*. Thus, it would have been expected at the time of the present invention that administration of tPA, even in the presence of aprotinin, would result in increased degradation of vWF and therefore decreased factor VIII half life.

Example 1 of the present application provides evidence that, surprisingly, use of tPA and aprotinin enhances factor VIII activity for up to 96 hours (*see* Example 1 and Figure1). Indeed, as noted above tPA and aprotinin surprisingly ***stabilize*** factor VIII in the absence of vWF.

In light of the expectation that tPA would enhance degradation of factor VIII and the surprising ability of tPA and aprotinin to stabilize factor VIII, the rejection of claims 1-4, 6, 7, 10 and 11 is improper and should be withdrawn.

The rejection of claims 1-6, 7, 8, 10 and 11 over the above references and further in view of Beguin *et al.* is also respectfully traversed. Beguin *et al.* is cited for teaching that vFW acts as a blood coagulator and as a carrier and stabilizer of factor VIII. The rejection provides no additional reasoning or evidence to show how Beguin *et al.* addresses the deficiencies of the references discussed above. In the absence of such a showing, the rejection is improper and should be withdrawn.

## CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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